discloses the dispersion having the highest percentage of drug (67%) exemplified by Applicants.

The Interview

As a further preliminary matter, Applicants' wish to thank Examiners Fubara and Gollamudi for the courteous and informative interview conducted with Applicants' representatives, Mr. DeKock and (the undersigned) Mr. Jones on October 11, 2005. As a partial response to matters raised at the interview, Applicants are herewith enclosing the declaration under 37 CFR 1.132 of Dwayne T. Friesen. It is respectfully submitted that the declaration addresses issues raised in both the interview and in the outstanding Office Action.

At the interview, the Examiners suggested the following: a) that since the proposed claim amendment to claim 1 is still drawn to generic subject, Applicants should show that different drugs will behave the same way when the ratio of drug and polymer are used; b) with regard to Miyajima, it was suggested to use column 3, lines 55-56 to compare the drug in Miyajima (NZ-105) at the same ratio of drug to polymer as the torcetrapib release profile presented by applicants in the interview.

As to point (a), it is respectfully submitted that the declaration is dispositive on the issue of whether different classes of drugs (i.e., acidic, basic, and neutral) behave similarly when formulated as a homogeneous spray dried solid amorphous dispersion with HPMCAS. All of the ten drugs tested, regardless of class, exhibited improved solubility, measured as the Maximum Supersaturated Concentration of dissolved drug (MSSC) achieved during the initial 90 minutes. Out of 10 drugs tested, five were neutral, three were basic, and two were acidic or weakly acidic. Regardless of the general classification of the particular drug tested (i.e., acidic, basic, or neutral), all of the drugs exhibited improved concentration enhancement with decreasing drug loading. The declaration thus demonstrates that the invention provides concentration enhancement to sparingly water-soluble drugs regardless of the particular sparingly water-soluble drug tested and/or its generic classification.

As to point (b), Applicants were unable to obtain a sample of NZ-105, the drug disclosed in Miyajima, for testing or evaluation. In its stead, Applicants offer data for nicardipine which was selected because, as between nicardipine and nifedipine, nicardipine has similar functional groups (tertiary amine and a substituted cyclic amine) as well as similar physical properties (solubility, logP, and melting point) relative to NZ-105. The

declaration shows similar behavior for nicardipine to that exhibited by the other compounds, including torcetrapib, for which test results were obtained, namely that, in general, improved concentration enhancement is obtained as drug loading decreases.

The declaration otherwise illustrates behavior that is exactly opposite to the teachings of Yamaguchi, one of two references that were used to make rejections. The significance of this is discussed in detail below.

The rejections and Applicants' traversal

Claims 1, 4-7, 10, 11, 13, 15, 17, 22, 39, 41-43, 45 and 47 and new claims 49-52 were rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (English Translation of Yakuzaigaku 53(4): 221-228, 1993). The Examiner stated, *inter alia*,

> Applicants argue that the drug is not molecularly dispersed in Yamaguchi; that Yamaguchi does not disclose that the drug is amorphous in the dispersion; that Yamaguchi does not disclose that the spray dried particles are solidified in less than 5 seconds and that the residual solvent content is less than 10 wt%; that Yamaguchi does not disclose a drug: HPMCAS of 1 to 0.2 to 1 to 100 which is 5:1 to 1:100. Applicants conclude by saying that Yamaguchi cannot anticipate the claims because so many elements required by Applicants' claims are missing.
>
> Applicants' argument is persuasive in part as the argument relates to the residual solvent, which is incorporated in the claims by amendment. The prior art discloses solid amorphous dispersion, Yamaguchi prepares the solid dispersion by spray drying and applicants form the molecular dispersion by spray drying. Thus the dispersion of Yamaguchi formed by spray drying is molecularly dispersed. Specifically, the only mention of "molecularly dispersed" in the examined application is in paragraph 0027 of the published application where it states, "it is generally preferred for the drug to be molecularly dispersed such that there is little or no drug present as separate amorphous domains." Yamaguchi, which forms solid amorphous dispersions of a drug by spray drying as does the instant application, does not mention that the drug is present as separate amorphous domains. The recitation of spray-dried particles solidifying in less than 5 seconds is not accorded patentable weight in a composition claim. However, both the prior art reference and the instant claims prepare the solid dispersions by spray drying. The claims are directed to compositions and the process of preparing the dispersions in both the examined claims and the prior art are the same. Applicants provided no showing indicating that the particles of Yamaguchi solidified in longer than 5 seconds and there is no unexpected results showing that the dispersion of the prior art formed by spray drying as does the claimed invention differs in any way from the claimed solid dispersion.
>
> Regarding the residual solvent, the prior art is silent and since applicants' dispersion spray dried as does the prior art contains residual solvent, it stands to reason that the solid dispersion of the prior art contains residual solvent. There is

no demonstration that the presence of the amount residual solvent recited in the claims provides unusual results. The rejection necessitated by the amendment follows.

Yamaguchi studies the solubility of solid dispersions of 4-0-(4-methoxmhenyllacetyltylosin (MAT) in carboxymethylethylcellulose (CMEC) or hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT®) and using the solid dispersions an increase of AUC and Cmax of greater than 2.5 fold was observed achieved (abstract). Yamaguchi prepares solid dispersions of MAT in CMEC, AQOAT or EC (ethylcellulose) by spray drying (item # 2 of page 2); the solubility of crystalline MAT is determined to be 0.002 at pH 6.8 (item 1 of page 4 and Table 1). In Figure 2 and at pH 4.0, Yamaguchi shows solid dispersions of MAT and CMEC or AQOAT in a ratio of 10:1 and concentration of the MAT in a use environment from AQOAT carrier matrix is about 650 µg and the concentration of amorphous MAT without a polymer in a use environment is about 220 µg; the ratio of the MAT from the AQOAT matrix to a control, such as the one without a polymer is at least greater than 1.5 and specifically about 2.95 (see page 5 and data extrapolated from Figure 2). Although, Yamaguchi exemplifies the dissolution studies with CMEC, the Yamaguchi reference also discloses MAT with AQOAT as is seen in the abstract, pages 2 (last line) and 5, and Figure 2. MAT bulk powder is used in the study in the preparation of the solid dispersion (page 2, item #1) and powder reads on amorphous.

Yamaguchi describes oral administration, fed state (i.e. "withholding food from the beagles from the night before the study") and measuring of blood concentration (page 4, item # 7 and page 10, item # 4), which description confers the implication of gastrointestinal tract environment and thus, this aspect of the disclosure reads on gastrointestinal tract use environment. Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQQAT dispersion. Specifically, paragraph 2, page 2 of translation states " MAT (100 g) and 50 g, 20 g,10 g or 5 g of CMEC were dissolved in 300 ml, of a 1:1 solvent mixture of methylene chloride and ethanol, then spraydried (SD-1; Tokyo Rikakikai) at an inlet temperature of 120 °C to form a powder. **Preparation was similarly carried out using AQOAT®** or EC as the carrier." Thus drug: polymer ratios of from 2:1, 5:1,10:1 and 20:1 are disclosed. [8/30/06 Office Action, pages 3-6, emphasis in the Office Action]

The rejection is traversed on the basis that Yamaguchi teaches away from Applicants' invention, and also fails to teach a dispersion that is homogeneous and in which the drug is amorphous.

Homogeneity in a dispersion can be demonstrated by Differential Scanning Calorimetry (DSC), as set forth in and explained by the Friesen declaration. More specifically, the declaration demonstrates that the higher the drug loading is in a dispersion, the more likely it is that the dispersion will contain a distinct drug phase. This point is illustrated by paragraph 10 which shows that, as drug loading increased above

50 wt% in torcetrapib/HPMCAS dispersions, the degree of phase separation also increased. Realizing that the term "homogeneous" refers to the uniformity of the dispersion, it will be appreciated that the more the drug in a drug/HPMCAS dispersion phase separates into an amorphous phase and a distinct drug phase, the less the dispersion is homogeneous. Thus the declaration, specifically Figure 11, demonstrates that the higher the drug loading is in a dispersion, the more likely it is that phase separation can occur. The declaration thus demonstrates that it becomes more likely to achieve homogeneity as drug loadings are lowered. This is important since, as generally demonstrated by Figure 11 in conjunction with Figures 1-10 of the declaration, lower drug loadings parallel increased homogeneity and improved concentration enhancement.

Yamaguchi teaches away from Applicants, including Applicants' teachings as discussed above. In Yamaguchi the lowest drug-to-polymer ratio disclosed is 67%, i.e., for the embodiment in which 100g of the drug MAT to 50 g of polymer were used. This lowest drug-to-polymer ratio disclosed in Yamaguchi corresponds to the upper limit of drug-to-polymer permitted by Applicants.

One of ordinary skill in the art would not find Applicants' invention obvious over Yamaguchi because Yamaguchi clearly teaches that better dispersions, i.e., better because they effect higher drug concentrations, are obtained as the drug loading is increased upward from 67%. See Figures 4 and 5 in Yamaguchi, both of which clearly demonstrate that drug dissolution from MAT/CMEC solid dispersions increased as the drug loading was increased. Thus the MAT/CMEC dispersion displaying the best (i.e., the highest) drug concentration over time in Figure 4 was the 10/0.5 drug:polymer dispersion (i.e., in which the drug-to-polymer was 20/1), indicating a drug loading slightly greater than 95%, the highest drug loading tested. The dispersion displaying the worst (i.e., lowest) concentration enhancement with time was the 10/5 dispersion in which the drug loading was 67%, the lowest drug loading tested. The clear conclusion to be drawn from Yamaguchi is that higher drug loadings correlate with higher (i.e., better) dissolved drug concentrations. One of ordinary skill in the art would not find it obvious from Yamaguchi to use a drug loading lower than 1:0.5 (i.e., Yamaguchi's 67% drug loading), the upper limit of Applicants' drug:polymer ratio range, because Yamaguchi clearly and directly teaches the opposite, i.e., that in order to enhance dissolved drug concentration, one should go to higher drug loadings.

That Yamaguchi teaches away from Applicants is underscored by the Friesen declaration submitted herewith. The declaration shows the results from experiments with a number of drugs that were neutral (i.e., non-ionizable), acidic and basic. The experiments included drugs that are disclosed in the application and drugs that are not. The declaration clearly demonstrates that (1) Applicants achieved better concentration enhancement as the drug loading was decreased; and (2) concentration enhancement is a general effect regardless of the drug's classification as acidic, basic, or neutral.

As an aside, it is noted that the Examiner accorded no patentable weight to the requirement that spray dried particles solidify within a certain time, stating that "...The recitation of spray-dried particles solidifying in less than 5 seconds is not accorded patentable weight in a composition claim." Applicants traverse the Examiner's statement on the basis that a process limitation can be of patentable significance, especially in the instant invention. Applicants teach that homogeneous drug dispersions are facilitated by rapid solvent removal, the more rapid the removal the better since dispersed drug has less chance to phase separate into drug-rich domains. The longer that solidification is allowed to proceed, the greater is the chance that drug-rich domains will form. Thus, Applicants maintain that the solidification time is important and indeed of patentable significance, particularly as Yamaguchi teaches nothing about it. The requirement certainly should not be ignored. In re Boe, 184 USPQ 38 (CCPA 1974). In simply deeming the solidification time requirement not to be of patentable weight, the Examiner failed to address this difference between Yamaguchi and Applicants, and did not consider the invention as a whole, as §103 requires.

Further, it is noted that Applicants have screened over 25 additional drugs and, with a single exception, have observed behavior as testified to in the declaration, namely that concentration enhancement generally increases as drug loading decreases, although curve shape can vary as demonstrated in the Figures. As to the one compound that constitutes the exception, the compound exhibited essentially no change in dissolution performance as a function of drug loading.

Applicants thus believe that concentration enhancement improves, *inter alia*, as drug loading is decreased and by spray drying under conditions ensuring that the solid amorphous dispersion is homogeneous. These teachings are not disclosed in Yamaguchi, which otherwise represents a distinct and unequivocal teaching away from the subject matter defined by Applicants' claims for the reasons discussed above. Clearly, one of ordinary skill who wanted to enhance the concentration of poorly soluble drugs would

not, based on Yamaguchi, use drug loadings less than 67% and would not realize that improved concentration enhancement can be achieved at lower drug loadings than Yamaguchi discloses. It is accordingly respectfully requested that the §103 rejection over Yamaguchi be withdrawn.

Claims 1, 7, 11, 13, 15, 23-26, 38, 39, 41-43, 45, 47 and new claims 49-52 were rejected under 35 USC 103 as unpatentable over Miyajima et al. (US 4,983,593). The examiner stated, in part:

> Applicants argue that Miyajima mentions spray drying only once in the entire disclosure, that Miyajima fails to describe solidification time of less than 5 seconds, that Miyajima does not disclose residual solvent and that Miyajima fails to disclose amorphous drug. Furthermore, applicants refer to excerpt from Remington that spray drying does not necessarily produce amorphous drug.
>
> Applicants' argument is persuasive in part as the argument relates to the residual solvent, which is incorporated in the claims by amendment. However, as referenced by applicants, the Remington reference does state that spray drying leads to "crystals and/or amorphous solids depending on the rate and conditions of solvent removal." Thus, the Remington reference further supports the fact that spray drying leads to amorphous products. It is respectfully noted that the invention is directed to a composition and a composition that is formed by spray drying. Applicants appear to imply that the spray dried product of Miyajima may or may not be amorphous, and if this is the case, it may also raise the question whether applicants product is amorphous since the claimed product is formed/prepared by spray drying. Although, applicants argue that Miyajima mentions spray drying only once in the disclosure and as such cannot be relied upon for spray drying, it is the Examiner's position that there is a disclosure of spray drying in Miyajima. The claims are composition claims. Solidification in less than 5 seconds would be inherent since both the prior art and the claims spray dry. Also, the recitation of spray-dried particles solidifying in less than 5 seconds is not accorded patentable weight in a composition claim. However, both the prior art reference and the instant claims prepare the solid dispersions by spray drying. The claims are directed to compositions and the process of preparing the dispersions in both the examined claims and the prior art are the same. Applicants provided no showing indicating that the particles of Miyajima solidified in longer than 5 seconds and there is no unexpected results showing that the dispersion of the prior art formed by spray drying as does the claimed invention differs in any way from the claimed solid dispersion.
>
> Regarding applicants' argument on claims 23-26, the examiner recognizes that
> obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is suggestion in Miyajima that the solubility of nifedipine, a poorly water-soluble drug, can be

improved and Miyajima provides the how to process for improving drugs that are sparingly soluble. [8/30/05 Office Action, pages 6-7]

Applicants' traverse the rejection on the basis that Miyajima does not suggest Applicants' claimed invention, nor teach how to achieve it. One of ordinary skill with knowledge of Miyajima would never realize the superior benefits that can be achieved via spray drying as opposed to rotary evaporation which is also a solvent processing method. Drying "*in vacuo*", is disclosed in the Miyajima examples.

As background, it is noted that Applicants' claimed invention requires a solid dispersion of drug and polymer that is homogeneous and in which the drug is amorphous. Miyajima mentioned the phrase "spray drying" once in his entire patent and never mentioned anything about spray drying again. Miyajima never disclosed an actual spray dried dispersion, let alone a solid amorphous spray dried dispersion, or how to achieve one. Miyajima does not teach the importance of low solidification times (less than 5 seconds) or low residual solvent contents (less than 10 wt%). In different words, Miyajima simply alludes to "spray drying" without ever teaching how to make a solid amorphous dispersion in which the drug is molecularly dispersed. Nor does Miyajima teach or suggest any of the factors that are important for making a homogeneous dispersion. The Remington article submitted with Applicants' previous response demonstrates that material made by spray drying can contain particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. The import of Remington is his confirmation that a spray dried material can contain crystalline solids, coupled with the fact that Miyajima never discloses how to make a spray-dried dispersion that is amorphous, as opposed to crystalline. The point here is that the mere mention of the phrase "spray drying" in Miyajima does not teach or make obvious a homogeneous solid amorphous dispersion as required by the instant claims. The point of Remington, and the reason that Applicants submitted the Remington article, is to show that **spray drying does not necessarily produce amorphous drug.** Miyajima contains zero disclosure otherwise as to how one of ordinary skill would make a polymer/drug dispersion in which the drug is amorphous, and as to what factors might be important if one wanted to do so. Given the lack of guidance in Miyajima, one of ordinary skill could just as easily make a spray dried material containing crystals, as confirmed in Remington, as make an amorphous dispersion, as required by Applicants. Only Applicants have provided such disclosure that details the requirements and that enables making an amorphous dispersion, and

those requirements are reflected in Applicants' claims. Miyajima, by contrast, provides no guidance that would lead one to make an amorphous dispersion, as opposed to a spray dried material that contains crystalline drug per Remington.

Further, Miyajima makes no distinction between dispersions produced for example, by vacuum evaporation and dispersions as claimed by Applicants. Miyajima exemplifies dispersions made using drying *in vacuo*, but discloses nothing about performance relative to dispersions produced by spray drying according to Applicants. Due, *inter alia*, to the fast solidification time and low residual solvent level required by Applicants, homogeneous dispersions made by spray drying effect better concentration enhancement than the relatively non-homogeneous dispersions made by a vacuum evaporation method. Applicants have conclusively demonstrated this point in the Examples of their specification and in the previous declaration of Dwayne T. Friesen, copy submitted herewith as Exhibit A, which was dated October 6, 2000 and submitted in parent application serial no. 09/131,019. See Applicants Example 24 and Comparative Example C9; Example 29 and C13 in the instant application, and the aforementioned prior declaration confirming that spray drying produces dispersions exhibiting better dissolution performance than rotary evaporation. One of ordinary skill would thus not find Applicants' solid amorphous dispersions obvious from Miyajima who says nothing about them.

Further, the Examiner has provided no basis supporting that one of ordinary skill would be motivated to modify the prior art in a way that would render Applicants' invention obvious. The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Laskowski, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989). It is respectfully submitted that no such motivation supporting the rejection was presented. Because the rejection does not detail reasoning that provides the motivation to modify the prior art, the rejection does not present a *prima facie* case of obviousness.

In summary, following are the reasons why Applicants are not obvious over Miyajima:

(a) Applicants distinguish over Miyajima because Applicants claim a homogeneous dispersion comprising amorphous drug. Miyajima neither discloses nor enables a homogeneous solid amorphous dispersion.

(b) Although Miyajima uses the phrase "spray drying", spray drying does not inherently produce amorphous drug. Remington states that spray drying may produce either amorphous or crystalline drug.

(c) Miyajima never disclosed an actual spray dried dispersion and makes no distinction between spray dried dispersions and dispersions produced by drying *in vacuo*. One of ordinary skill in the art would never realize the superior performance of Applicants invention, which is submitted to be unexpected based on Miyajima.

None of the points discussed above would be appreciated by one of ordinary skill in the art based on Miyajima. Withdrawal of the rejection under 35 USC §103(a) over Miyajima is accordingly respectfully requested.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited. The Commissioner is hereby authorized to charge any additional fees which may be required, or to credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

Date: FEBRUARY 28, 2006

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